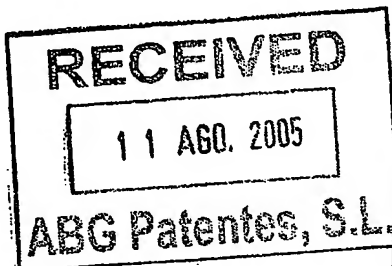


PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

09.08.2005

Applicant's or agent's file reference
P1254PC00

IMPORTANT NOTIFICATION

International application No.
PCT/ES2003/000510

International filing date (day/month/year)
08.10.2003

Priority date (day/month/year)
08.10.2003

Applicant
INNOVAPROTEAN, S.L. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80298 Munich
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Authorized Officer

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1254PC00	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/ES2003/000510	International filing date (<i>day/month/year</i>) 08.10.2003	Priority date (<i>day/month/year</i>) 08.10.2003
International Patent Classification (IPC) or both national classification and IPC C07C65/05		
Applicant INNOVAPROTEAN, S.L. et al.		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of 5 sheets, including this cover sheet.
	<input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
	These annexes consist of a total of sheets.
3.	This report contains indications relating to the following items: <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 21.03.2005	Date of completion of this report 09.08.2005
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>	Authorized Officer Heibl, C Telephone No. +49 89 2399-8331



- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/ES2003/000510**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-9
	No: Claims	
Inventive step (IS)	Yes: Claims	1-9
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1 - WO-A 98/46234

D2 - EP-A 082 404

D3 - WO-A 98/20864

The present invention provides 'diflunisal' derivatives having use as inhibitors of the formation of amyloid fibrils associated with transthyretin (amyloidogenesis inhibitors), thus being suitable for the treatment of neurogenerative diseases.

The present compounds of formula (I) (see claim 1) are in particular characterized by having a **iodine** substituent in **5-position** of the basic molecule (2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid). Since none of the prior art documents D1-D3 discloses such **5-iodo** derivatives, the claimed compounds (claims 1-3) and the subject-matter of claims 4-9 related herewith can be considered novel (Art. 33(2) PCT).

The effect of said iodation leading to an enhanced activity (amyloidogenesis inhibition) as compared to non-iodated derivatives (see the experimental part of the present application) cannot be derived from the teaching of the available prior art documents. Indeed, D1 which merely theoretically covers iodo derivatives of certain diflunisal ester derivatives (see the definition of R_3 which includes inter alia "halo", the position of R_3 being not defined) relates to compounds having anti-platelet activity, hydroxy radical scavenging properties which makes them suitable for the treatment or control of thrombosis and ischaemic/perfusion injury of tissues such as liver.

D2 deals with analgesic and anti-inflammatory diflunisal derivatives, D3 with anti-inflammatory diflunisal derivatives which are also suitable for the treatment of neurogenerative diseases. In addition, neither D2 nor D3 suggests iodination of diflunisal derivatives.

Having regard to the prior art, the subject-matter of claims 1-9 is also considered to meet the requirements of Art. 33(3) PCT.

The subject-matter of claims 1-9 also meets the criteria Art. 33(4) PCT (industrial

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/ES2003/000510

applicability).